

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) **EP 0 817 809 B1**

(12)

## EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention  
of the grant of the patent:  
31.07.2002 Bulletin 2002/31

(51) Int Cl.7: **C08G 77/26**, A61B 5/00,  
C08G 18/61, C08G 77/458,  
C12Q 1/00

(21) Application number: **96911389.3**

(86) International application number:  
**PCT/US96/03987**

(22) Date of filing: **25.03.1996**

(87) International publication number:  
**WO 96/30431 (03.10.1996 Gazette 1996/44)**

(54) **HOMOGENOUS POLYMER COMPOSITIONS CONTAINING SILICONE FOR BIOSENSOR  
MEMBRANES**

HOMOGENE POLYMERZUSAMMENSETZUNGEN DIE SILICON ENTHALTEN FÜR  
BIOSENSORMEMBRANEN

COMPOSITIONS DE POLYMERES HOMOGENES CONTENANT DE LA SILICONE POUR  
MEMBRANES DE BIODETECTEURS

(84) Designated Contracting States:  
**AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC  
NL PT SE**

(72) Inventor: **VAN ANTWERP, William, P.**  
Valencia, CA 91355 (US)

(30) Priority: **27.03.1995 US 410775**

(74) Representative: **Goldin, Douglas Michael**  
**J.A. KEMP & CO.**  
14 South Square  
Gray's Inn  
London WC1R 5JJ (GB)

(43) Date of publication of application:  
**14.01.1998 Bulletin 1998/03**

(73) Proprietor: **Medtronic MiniMed, Inc.**  
Northridge, CA 91325-1219 (US)

(56) References cited:  
**US-A- 5 214 119** **US-A- 5 238 732**  
**US-A- 5 239 036** **US-A- 5 239 037**

**EP 0 817 809 B1**

**BEST AVAILABLE COPY**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

## Description

[0001] This invention relates generally to biosensor materials. More specifically, this invention relates to a novel polymeric material that is useful as an outer biocompatible membrane for use in biosensor applications.

[0002] Biosensors are devices that use biological materials (cells, enzymes, tissues etc.) to convert a chemical concentration in a matrix into a detectable signal (electrical, acoustic, optical, thermal etc.). There are many types of biosensors used for a wide variety of analytes. Electroenzymatic biosensors which use enzymes to convert a concentration to an electrical signal have been the most studied types of biosensors. For a review of some of the operating principles of biosensors, see P. Bergveld, and D. Thevenot, Advances in Biosensors, Supplement 1, p. 31-94, A.P.F. Turner, editor.

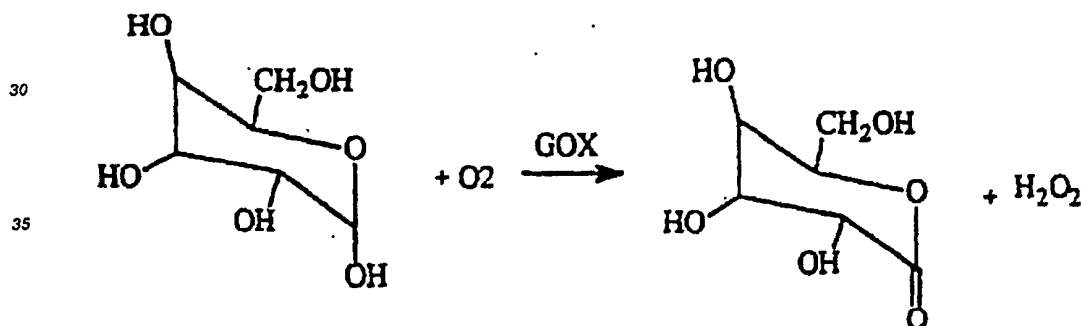
[0003] US-A-5 239 036 discloses a waterproof polyurethane membrane designed primarily for use in making waterproof clothing.

[0004] US-A-5 214 119 discloses a blockcopolymer in the form of a polyurethane with silicone linkages.

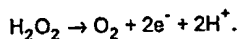
[0005] The prototype biosensor is the amperometric glucose sensor. There are several reasons for the wide ranging interest in glucose sensors. The scientific interest is driven by the availability of a very robust enzyme, glucose oxidase, which is used to monitor glucose, as well as the desire to develop model sensors for a wide variety of analytes. The commercial interest is driven by the need for glucose monitoring of patients with diabetes mellitus as well as the development of sensors that can be used to monitor fermentation reactions in the biotechnology arena. A working glucose sensor is also the most difficult component in development of a closed loop artificial pancreas with an implanted insulin pump.

[0006] Any amperometric glucose sensor or any oxido-reductase enzyme that uses  $O_2$  as a co-substrate that is designed for subcutaneous or intravenous use requires an outer membrane and an anti-interference membrane because of the fundamental nature of the sensor and the environment in which the measurement is made.

[0007] A glucose sensor works according to the following chemical reaction (Equation 1):



[0008] In this reaction, glucose reacts with oxygen in the presence of glucose oxidase (GOX) to form gluconolactone and hydrogen peroxide. The gluconolactone reacts with water to open the lactone ring and produce gluconic acid. The  $H_2O_2$  reacts electrochemically as shown below (Equation 2):



[0009] The current measured by the sensor/potentiostat (+0.5 to +0.7 V oxidation at Pt black electrode) is due to the two electrons generated by the oxidation of the  $H_2O_2$ . Alternatively, one can measure the decrease in the oxygen by amperometric measurement (-0.5 to -1 V reduction at Pt black electrode).

[0010] The stoichiometry of Equation 1 clearly demonstrates some of the problems with an implantable glucose sensor. If there is excess oxygen for Equation 1, then the  $H_2O_2$  is stoichiometrically related to the amount of glucose that reacts at the enzyme. In this case, the ultimate current is also proportional to the amount of glucose that reacts with the enzyme. If there is insufficient oxygen for all of the glucose to react with the enzyme, then the current will be proportional to the oxygen concentration, not the glucose concentration. For the sensor to be a true glucose sensor, glucose must be the limiting reagent, i.e. the  $O_2$  concentration must be in excess for all potential glucose concentrations. This means that a way must be devised to either increase the  $O_2$  in the GOX membrane, decrease the glucose con-

centration, or devise a sensor that does not use O<sub>2</sub>.

[0011] The basic problem in the use of a biosensor in the body is that the ratio of glucose to O<sub>2</sub> is opposite to what is desired for optimal operation of the biosensor. The glucose concentration in the body of a diabetic patient can vary from 2 to 30 mM (millimoles per liter or 36 to 540 mg/dl), whereas the typical oxygen concentration in the tissue is 0.02 to 0.2 mM. U. Fischer, A. Hidde, H. von W oedtke, K. Rebrin, and P. Abel, Biomed. Biochim. Acta., 1989, Vol. 48, pp. 965-971. This ratio in the body means that the sensor would be running in the Michaelis Menten limited regime and would be very insensitive to small changes in the glucose concentration. This problem has been called the "oxygen deficit problem".

[0012] Several approaches to solving the deficit problem have been attempted in the past. The simplest approach is to make a membrane that is fully O<sub>2</sub> permeable, with no glucose permeability and mechanically perforate it with a small hole that allows glucose to pass. Here the differential permeability is defined by the ratio of the small hole area to the total membrane area. Two significant problems with this method are first that reproducibly making small holes is difficult and second and more serious, the O<sub>2</sub> permeability is a strong function of the thickness of the membrane and thickness is difficult to control in mass production. Microporous membranes (U.S. Patent No. 4,759,828 to Young et al.) have also been tried with limited success. Another problem with both the hole in the membrane approach and the microporous membrane approach is that the sensor electrodes and the enzyme layer are exposed to body fluids. Body fluids contain proteins that coat the electrodes leading to decreased sensitivity of the sensor and enzymes (proteases) that can digest or degrade the sensor active enzyme.

[0013] One approach to the oxygen deficit problem is described by Gough (U.S. Patent No. 4,484,987). The approach uses a combination membrane with discrete domains of a hydrophilic material embedded in a hydrophobic membrane. In this case, the membrane is not homogenous and manufacturing reproducibility is difficult. Physical properties of the membrane are also compromised. In a similar manner, Gough (U.S. Patent No. 4,890,620) describes a "two dimensional" system where glucose diffusion is limited to one dimension while the oxygen diffusion is from both dimensions. This sensor is extremely complicated and manufacturing on a large scale is expected to be difficult.

[0014] Several other groups, G.W. Shaw, D.J. Claremont and J.C. Pickup, Biosensors and Bioelectronics, 1991, Vol. 6, pp. 401-406; D.S. Bindra, Y. Zhang, G.S. Wilson, R. Stenberg, D.R. Thevenot, D. Moatti and G. Reach, Analytical Chemistry, 1991, Vol. 63, p. 1692; and M. Shichiri, Y. Yamasaki, K. Nao, M. Sekiya and N. Ueda, Horm. Metab. Res., Suppl. Ser., 1988, Vol. 20, p. 17, have used a homogenous membrane of a relatively hydrophobic polyurethane and reported good results. In classical diffusion experiments with these membranes, however, the glucose diffusion is extremely small. It is believed that the ability of these polyurethane layers to allow glucose diffusion is due to micro cracks or micro holes in these materials when applied as membranes.

[0015] In order to circumvent the oxygen deficit problem with a homogenous membrane, Allen et al. developed two homogenous membranes with both hydrophilic and hydrophobic regions. In U.S. Patent No. 5,284,140, they describe an acrylic system and in U.S. Patent No. 5,322,063 they describe a polyurethane system. Both of the membranes have hydrophilic and hydrophobic moieties in the molecule leading to limited control of oxygen and glucose permeabilities.

[0016] The key to stable, high sensitivity enzyme biosensors is that the sensor output must be limited only by the analyte of interest, not by any co-substrates or kinetically controlled parameters such as diffusion. In order to maximize the output current (equation 2) of the biosensor, oxygen diffusion should be as large as possible while maintaining oxygen excess at the reaction surface. Since the normal concentration of O<sub>2</sub> in the subcutaneous tissue is quite low, maximization of the O<sub>2</sub> diffusion coefficient is desirable.

[0017] The membrane systems described in the literature as cited above attempt only to circumvent the oxygen deficit problem by reducing the amount of glucose diffusion to the working electrode of the biosensor. The magnitude of the signal from a typical biosensor of the appropriate size for either subcutaneous or intravenous implantation is typically 1 to 10 nA at physiological glucose and O<sub>2</sub> concentrations. This level of current requires sophisticated electronics for measurement. Increasing the oxygen transport and concomitant glucose transport will increase the signal and (to a limited extent) reduce the complexity of the controlling and recording electronics. It is obvious however that a membrane that simultaneously increased the oxygen and limited the glucose would lead to both better performance and increased signal.

[0018] Accordingly, there has been a need for a polymer useful in an outer polymeric membrane of a biosensor. There is a need for the membrane to have physical stability and strength, adhesion to the substrate, processability (ability to be synthesized/manufactured in reasonable quantities and at reasonable prices), biocompatibility, ability to be cut by laser ablation (or some other large scale processing method), and compatibility with the enzyme as deposited on the sensor. The present invention fulfills these needs and provides other related advantages.

[0019] Thus, the invention provides a homogenous polymer composition which is permeable to glucose and water and which is useful as a membrane for biosensors, comprising the reaction products of at least one diisocyanate, at least one hydrophilic diol or diamine (and optionally at least one hydrophobic aliphatic diol or diamine), and at least one silicone material.

[0020] The invention also provides an implantable biosensor for measuring the reaction of an analyte and oxygen,

comprising the composition of the invention. The hydrophilic diamine may comprise silicone. The composition may also contain at least one short chain aliphatic diamine and/or diol. This polymer composition is useful as an outer biocompatible membrane for use in biosensors. The membranes thus formed allow for increasing oxygen permeability and decreased analyte (e.g. glucose) permeability. They also possess the necessary properties for an outer polymeric membrane.

[0021] Possible amounts of the various reaction products are, for example  
 about 50 more percent diisocyanate;  
 5 to 45 more percent hydrophilic diol or diamine;  
 5 to 45 mole percent aliphatic diol or diamine; and  
 5 to 40 mole percent silicone material.

[0022] Other features and advantages of the present invention will become apparent from the following more detailed description taken in conjunction with the accompanying drawings which illustrate, by way of example, the principles of the invention.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0023] The accompanying drawings illustrate the invention. In such drawings:

FIGURE 1 shows the polymerization reaction of a diisocyanate and a diol to make a urethane linkage and the reaction of the diisocyanate and a diamine to make a urea linkage.

FIGURE 2 shows exemplary diisocyanates used as a first component in a polymer composition of the present invention.

FIGURE 3 shows exemplary silicones used as a second component in the polymer composition of the present invention.

FIGURE 4 shows exemplary long chain hydrophilic diols and diamines used as a third component in the polymer composition of the present invention.

FIGURE 5 shows exemplary short chain aliphatic diols and diamines that may be used in the polymer composition of the present invention.

FIGURE 6 shows an infrared spectrum of an exemplary polyurea composition of the present invention.

FIGURE 7A is a schematic top view of an exemplary glucose sensor having electrodes covered with an exemplary polymer of the present invention.

FIGURE 7B is a sectional side view of a working electrode covered with layers of enzyme and the polymer composition.

FIGURE 8 is a graph showing sensor output in various glucose solutions as a measure of time.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0024] In a preferred embodiment, the proposed membrane for the sensor incorporates two different types of bonds and components into a single polymer. The type of polymer is a polyurethane polyurea. The chemistry of the polymerization is shown in Figure 1 in a simplistic manner. The reactions shown in Figure 1 show the reaction of a diisocyanate and a diol to make a urethane linkage and the same isocyanate reacting with a diamine to make a urea linkage. In alternative embodiments, the polymer may contain either the urea or the urethane linkage depending on the individual components used.

[0025] The polymer composition described in this invention is synthesized from three or four individual components. The basic building blocks for attachment are the exemplary diisocyanates shown in Figure 2. These are the preferred diisocyanates for the membranes of this invention, however aromatic diisocyanates can be used if appropriate care is used to remove all of the toxic monomer from the final polymer.

[0026] Two other components are used for the final membrane polymer. The first is a silicone material (siloxane) that has excellent O<sub>2</sub> permeability. These siloxanes do not have H<sub>2</sub>O permeability so that they do not allow any glucose diffusion. A polydimethyl siloxane polymer with reactive endgroups is the preferred constituent of the polymer. Figure

3 shows some of the potential siloxanes that have been incorporated into biosensor membranes.

[0027] Another component of the polyurethane/polyurea polymer composition is a long chain hydrophilic diol or diamine that incorporates water permeability into the polymer. Several water permeable diols and diamines have been used in the membranes and are shown in Figure 4. These include diols like polyethylene glycol (PEG) or polypropylene glycol (PPG) and diamines of the same type. Of course, anyone skilled in the art realizes that many other diol or diamines could be substituted.

[0028] In the preliminary data, the diol used is PEG 400 or PEG 600 which is very hydrophilic and leads to good H<sub>2</sub>O transport. For the diamine a silicone material can be used. Of course, the silicone material could be a diol as well, but stable diol terminated silicones are not readily commercially available.

[0029] The silicone has excellent O<sub>2</sub> transport while the diol can be tailored to control the H<sub>2</sub>O transport and hence the glucose permeability. The use of silicone can easily increase the O<sub>2</sub> transport by a factor of five, increasing the maximal glucose permeability by 5 fold as well. Since the biosensors as constructed are kinetically limited, it is difficult to predict the exact increase in currents generated by the sensors.

[0030] It is sometimes necessary when synthesizing a polyurethane material to incorporate a short chain diol or diamines that would lend physical strength to the polymer but not increase its basic glucose permeability. In these cases, the diols and diamines shown in Figure 5 have been used. Other short chain aliphatic diamines and diols could easily be substituted by one skilled in the art.

[0031] Since the siloxanes have excellent oxygen permeability and no glucose permeability, the short chain diols and diamines have fair oxygen permeability with no glucose permeability, and the long chain diols and diamines have excellent glucose permeability and good oxygen permeability, the final polymer can easily be tailored to a specific ratio of oxygen to glucose permeability. Although the ratio is the most important variable for proper glucose sensor operation, the magnitudes of the diffusion coefficients are also important since the magnitudes of the individual diffusion coefficients determine the final currents produced by a sensor and the higher the currents the easier are the electronics.

[0032] Polymerization was carried out in either solution or by bulk polymerization. In all cases, there are equal molar quantities of the diisocyanate on the one hand and the combination of the diol + diamine + short chain aliphatic diol or diamine on the other. Solution polymerization was carried out in either dimethylformamide (DMF) or tetrahydrofuran (THF).

[0033] Since water is reactive with the diisocyanates and can lead to shorter chain polymers than is optimal, precautions were taken to ensure that all solvents, reactants and glassware were as dry as possible. Short and long chain diols and long chain diamines were dried by azeotropic distillation from toluene. Aliphatic diamines were distilled from molecular sieves. Solvents were dried by distillation from CaH or molecular sieves as appropriate. Glassware was flame dried after assembly and before introduction of the reactants. Diisocyanates and siloxanes were used as received or stored over molecular sieves.

[0034] Polymerization of polyurethane/polyureas can be carried out without catalyst but in the preferred embodiment, dibutyltin bis(2-ethylhexanoate) is added in trace amounts. Bulk polymerization was usually started at about 50 degrees Celsius and when all components were mixed together, an exotherm reaction was observed to about 95 degrees Celsius in the flask. After the initial exotherm reaction, the temperature was maintained at 60 degrees Celsius to 80 degrees Celsius for about 4 hours.

[0035] Solution polymerization was carried out the same way, with the exotherm reaction only rising to 75 degrees Celsius. Solution polymerization was carried out for 12 hours (overnight) at between 50 degrees Celsius and 75 degrees Celsius.

[0036] After polymerization was complete, the reaction mixture was transferred to a large volume (5 liters or more) of rapidly stirred DI (deionized) water. The polymer that precipitated in the water was cut in small pieces and dried at 50 degrees Celsius to a constant weight.

[0037] In order that those skilled in the art can more fully understand this invention, the following examples are set forth. These examples are given solely for purposes of illustration, and should not be considered as expressing limitations unless so set forth in the appended claims. All parts and percentages are by weight, unless otherwise stated.

#### EXAMPLE 1

##### Bulk Polymerization

[0038] 4.44 grams (30 mmole, 100 mole %) of isophorone diisocyanate dried over molecular sieves were transferred to a 100 ml round bottom flask fitted with a nitrogen purge line and reflux condensor. 2.40 grams (4 mmole, 20 mole %) of PEG 600 dried via toluene distillation, 1.06 grams (10 mmole 50 mole %) of diethylene glycol dried via toluene distillation and 15 grams (6 mmole, 30 mole %) of aminopropyl terminated polydimethyl siloxane MW 2500 were added to the flask. Heating via heating mantle was started until 50 degrees Celsius was obtained. At this point about 15 mg of dibutyltin bis(2-ethylhexanoate) was added to the flask and the temperature rose to about 95 degrees Celsius. The

solution was stirred continuously. The solution was then heated at 65 degrees Celsius for 4 hours during which time it became increasingly viscous. The polymer was dissolved in 50 ml of hot THF and the solution was allowed to cool. After cooling, the entire solution was poured into 5 liters of stirring DI water. The precipitated polymer was torn into small pieces and dried at 50 degrees Celsius until constant weight.

5

## EXAMPLE 2

Solution Polymerization

- 10 [0039] 1.34 grams (8 mmole, 100 mole %) of dried 1,6 hexamethylene diisocyanate were added to a 100 ml 3 neck flask containing 20 ml of dry THF. 0.8 grams (4 mmole, 50 mole %) of dried PEG 200 were added with stirring. 10 grams (4 mmole, 50 mole %) of aminopropyl terminated polydimethyl siloxane MW 2500 were added. Heating via heating mantle was started until 50 degrees Celsius was obtained. At this point about 15 mg of dibutyltin bis(2-ethyl-hexanoate) were added to the flask and the temperature rose to about 83 degrees Celsius. The mixture was heated  
15 at 70 degrees Celsius for 12 hours and cooled. During heating the solution became very viscous, enough to stop the mechanical stirrer. The cooled solution was poured into three liters of rapidly stirred DI water and the precipitated polymer was washed with DI water three times, torn into small pieces and dried at 50 degrees Celsius until constant weight.
- [0040] Membranes for testing purposes were cast several ways. In some cases, membranes were cast from THF or DMF/CH<sub>2</sub>Cl<sub>2</sub> (2/98 vol. %) onto glass plates using a parallel arm Gardner knife. The dried films were removed, hydrated fully and their thickness measured with a micrometer. In other cases, films were cast from solution onto filtration membranes of known thickness. It is assumed in the measurements reported below that the membrane material completely filled the pores of the filtration membranes and that the thickness of the filtration media is the thickness of the membrane.
- 25 [0041] An infrared spectrum of the product of Example 2 showing the expected bands is shown in Figure 6.
- [0042] Water pickup was measured gravimetrically. Diffusion coefficients were measured using Fick's first law of diffusion in a standard permeability cell (Crown Glass Co.) at 37±0.2 degrees Celsius. The polymer may absorb for example between 10% to 80% water at that temperature, and especially between 20% to 70%. The mathematics of diffusion are beyond the scope of this document however a brief outline is appropriate.
- 30 [0043] Flux = -D dc/dx is the basic diffusion equation. Here D is the diffusion coefficient which is a physical property of both the solute and the material in which it is diffusing. In other words, D is not a property of a molecule or polymer, but is a property of the system so the system needs to be fully described for the measurement to be put in context. dc/dx is the concentration gradient, dc, over the thickness of the membrane, dx. The minus sign simply denotes that the diffusion is toward the region of lower concentration. If mass balance is considered, Fick's second law of diffusion may  
35 be generated, dc/dt = D d<sup>2</sup>c/dx<sup>2</sup>. By assuming Dirichlet boundary conditions, this equation can be solved using Laplace transform techniques.
- [0044] The oxygen diffusion coefficients were measured by securing the membrane between two glass cells (Crown Glass) with a rubber gasket. Both cells were filled with phosphate buffered saline (PBS) (0.1 M NaCl, 0.05 M phosphate pH 7.4). One cell was sparged with room air (20% O<sub>2</sub> assumed) and one side was sparged with HPLC grade He. An  
40 oxygen electrode (Microelectrodes) was placed in each cell. The oxygen electrode outputs were connected to a microcomputer controlled data acquisition system and the oxygen concentration from both cells was recorded as a function of time.
- [0045] Glucose diffusion coefficients were obtained in a similar manner except that one side was filled with 400 mg/dl glucose solution in PBS while the other side was filled with PBS containing no glucose. The concentrations of glucose  
45 on both sides of the membranes were measured with a YSI glucose analyzer at 5 minute intervals until equilibrium was obtained.
- [0046] The curves of concentration vs. time were inputted into a microcomputer and the diffusion coefficients were calculated using the entire curve. Curve fits generally had correlation coefficients (R<sup>2</sup>) better than 0.95.
- 50 [0047] Table 1 below shows some of the results for a variety of polymers prepared according to the methods described above.

55

Table 1

Five Representative Polymer Formulations				
Polymer	Diisocyanate	Hydrophilic	Aliphatic	Siloxane
		Diol	Diol	
1	1-6 Hexamethylene	PEG 600 20%	DEG 60%	Aminopropyl 20%
2	Isophorone	PEG 600 20%	DEG 50%	Aminopropyl 30%
3	1-6 Hexamethylene	PEG 600 50%	None	Aminopropyl 50%
4	1-6 Hexamethylene	PEG 400 40%	None	Aminopropyl 60%
5	1-6 Hexamethylene	PEG 600 60 %	None	Aminopropyl 40%

[0048] Table 2 give some of the physical and chemical properties of the polymers listed above.

Table 2

Physical Properties of Representative Polymers			
Polymer	Water Pickup	D O <sub>2</sub>	D Glucose
	%	x10 <sup>-6</sup> cm <sup>2</sup> /sec	x 10 <sup>-9</sup> cm <sup>2</sup> /sec
1	28.5	1.21	18.5
2	31.3	0.57	55.7
3	44	1.50	105
4	57	1.22	13.5
5	71	1.45	155

[0049] A membrane made from the polymer identified as number 3 above has excellent mechanical properties as well as appropriate oxygen and glucose diffusivities. In order to test this membrane, a prototype glucose sensor generally designated in accompanying drawing FIGURE 7A by the reference number 10 was built. The sensor 10 contains a reference electrode 12, a working electrode 14, and a counter electrode 16 deposited on a polymeric sheet 19. A series of bonding pads 18 complete the sensor 10. As shown in FIGURE 7B, the working electrode 14 was covered with a layer 20 of the enzyme glucose oxidase and the entire electrode array was coated with a layer 22 of the polymer by dip coating two times from a 5 wt % solution of the polymer in THF. The sensor was connected to a commercial potentiostat (BAS Instruments) (not shown) and operated with a potential of +0.6 volts between the working electrode and the reference electrode.

[0050] Glucose response is shown in Figure 8. As seen in Figure 8, the response of the electrode system is linear over the physiological glucose range, suggesting relative independence of local O<sub>2</sub> concentration. All of the other polymers tested show similar behavior to the polymer identified as number 3 shown in Figure 8 and are acceptable as membranes for biosensor applications. While the principles of the invention may be used in the fabrication of membranes for glucose sensors, the invention is not as limited. Indeed, the membrane in accordance with the invention may be used for the detection of a large number of analytes.

## Claims

1. A homogenous polymer composition which is permeable to glucose and water and which is useful as a membrane for biosensors, comprising the reaction products of at least one diisocyanate, at least one hydrophilic diol or diamine, and at least one silicone material.
2. The homogenous polymer composition of claim 1, further comprising at least one hydrophobic aliphatic diol or diamine in the reaction products.

3. The composition of claim 1, wherein said polymer absorbs between 10% to 80% water at 37 degrees Celsius.
4. The composition of claim 1, wherein said diisocyanate is selected from the group consisting of isophorone, 1,6-hexamethylene or 4,4'-methylenebis (cyclohexyl isocyanate).
5. The composition of claim 1, wherein said hydrophilic diol or diamine is selected from the group consisting of polyethylene glycol, polypropylene glycol, amino-terminated polyethylene glycol, amino acid esters terminated polyethylene glycol, and block copolymers of polyethylene glycol and polypropylene glycol.
6. The composition of claim 2, wherein said aliphatic diol or diamine is selected from a group consisting of ethylene glycol, propylene glycol, 1-3 propanediol, and 1-3 diaminopropane.
7. The composition of claim 1, wherein said silicone material is selected from the group consisting of amino propyldimethyl terminated siloxane, carboxy propyl-dimethoxy terminated siloxane and carbinol terminated siloxane.
8. The composition of claim 2, wherein the polymer is obtained from the reaction products of about 50 mole percent diisocyanate, 5 to 45 mole percent hydrophilic diol or diamine, 5 to 45 mole percent aliphatic diol or diamine, and 5-40 mole percent silicone material.
9. The composition of claim 5, wherein the polyethylene glycol has an average molecular weight of 600.
10. The composition of claim 3, wherein said polymer absorbs between 20% to 70% water at 37 degrees Celsius.
11. The composition of claim 1, wherein the hydrophilic diamine comprises silicone.
12. An implantable biosensor for measuring the reaction of an analyte and oxygen, said biosensor having a biocompatible membrane for controlling the permeability of analyte and oxygen to the biosensor elements, said membrane comprising a homogenous polymer composition which is permeable to glucose and water comprising the reaction products of at least one diisocyanate, at least one hydrophilic diol or diamine, and at least one silicone material.
13. The biosensor of claim 12, wherein the analyte comprises glucose.
14. The biosensor of claim 13 wherein the homogenous polymer composition further comprises at least one aliphatic diol or diamine added to the reaction.
15. The biosensor of claim 14, wherein the polymer comprises from 50 mole percent diisocyanate, 5 to 45 mole percent hydrophilic diol or diamine, 5 to 45 mole percent aliphatic diol or diamine, and 5-40 mole percent silicone material.
16. The biosensor of claim 12, wherein the homogeneous polymer composition is as defined in any of claims 3 to 7 and 9 to 11.

#### Patentansprüche

1. Eine homogene Polymerzusammensetzung, die gegenüber Glucose und Wasser permeabel ist und die als Membran für Biosensoren geeignet ist, umfassend die Produkte der Umsetzung mindestens eines Diisocyanats, mindestens eines hydrophilen Diols oder Diamins und mindestens eines Silikonmaterials.
2. Homogene Polymerzusammensetzung nach Anspruch 1, bei der weiter mindestens ein hydrophobes aliphatisches Diol oder Diamin umgesetzt wird.
3. Zusammensetzung nach Anspruch 1, bei der das Polymer bei 37°C 10 % bis 80 % Wasser absorbiert.
4. Zusammensetzung nach Anspruch 1, bei der das Diisocyanat aus der Gruppe bestehend aus Isophorondiisocyanat, 1,6-Hexamethylen-diisocyanat und 4,4'-Methylenbis(cyclohexylisocyanat) ausgewählt ist.
5. Zusammensetzung nach Anspruch 1, bei der das hydrophile Diol oder Diamin aus der Gruppe bestehend aus Polyethylenglycol, Polypropylenglycol, Polyethylenglycol mit endständigen Aminogruppen, Polyethylenglycol mit



endständigen Aminosäureestern und Blockcopolymeren von Polyethylenglycol und Polypropylenglycol ausgewählt ist.

6. Zusammensetzung nach Anspruch 2, bei der das aliphatische Diol oder Diamin aus der Gruppe bestehend aus Ethylenglycol, Propylenglycol, 1,3-Propanediol und 1,3-Diaminopropan ausgewählt ist.
7. Zusammensetzung nach Anspruch 1, bei der das Siliconmaterial aus der Gruppe bestehend aus einem Siloxan mit endständigen Aminopropyl-dimethylgruppen, einem Siloxan mit endständigen Carboxypropyl-dimethoxygruppen und einem Siloxan mit endständigen Carbinolgruppen ausgewählt ist.
8. Zusammensetzung nach Anspruch 2, bei der das Polymer aus den Produkten der Umsetzung von etwa 50 mol-% Diisocyanat, 5 bis 45 mol-% eines hydrophilen Diols oder Diamins, 5 bis 45 mol-% eines aliphatischen Diols oder Diamins und 5 bis 40 mol-% eines Siliconmaterials erhalten wird.
9. Zusammensetzung nach Anspruch 5, bei der das Polyethylenglycol ein durchschnittliches Molekulargewicht von 600 aufweist.
10. Zusammensetzung nach Anspruch 3, bei der das Polymer bei 37°C 20 % bis 70 % Wasser absorbiert.
11. Zusammensetzung nach Anspruch 1, bei der das hydrophile Diamin ein Silicon umfasst.
12. Ein implantierbarer Biosensor zur Messung der Reaktion eines Analyten und Sauerstoff, wobei der Biosensor eine biologisch verträgliche Membran zur Steuerung der Permeabilität des Analyten und von Sauerstoff zu den Elementen des Biosensors aufweist, wobei die Membran eine homogene Polymerzusammensetzung umfasst, die gegenüber Glucose und Wasser permeabel ist und welche die Produkte der Umsetzung mindestens eines Diisocyanats, mindestens eines hydrophilen Diols oder Diamins und mindestens eines Siliconmaterials umfasst.
13. Biosensor nach Anspruch 12, bei dem der Analyt Glucose umfasst.
14. Biosensor nach Anspruch 13, bei dem die homogene Polymerzusammensetzung weiter mindestens ein aliphatisches Diol oder Diamin umfasst, das der Umsetzung zugesetzt wird.
15. Biosensor nach Anspruch 14, bei dem das Polymer 50 mol-% Diisocyanat, 5 bis 45 mol-% eines hydrophilen Diols oder Diamins, 5 bis 45 mol-% eines aliphatischen Diols oder Diamins und 5 bis 40 mol-% eines Siliconmaterials umfasst.
16. Biosensor nach Anspruch 12, bei dem die homogene Polymerzusammensetzung gemäß einem der Ansprüche 3 bis 7 und 9 bis 11 definiert ist.

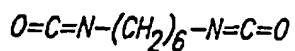
#### Revendications

1. Composition homogène de polymères, perméable au glucose et à l'eau et utilisée en tant que membrane pour des bio-capteurs comprenant les produits de réaction d'au moins un diisocyanate, un diol ou une diamine hydrophile et un silicone.
2. Composition homogène de polymères selon la revendication 1, comprenant par ailleurs au moins un diol ou une diamine aliphatique hydrophobe dans les produits de réaction.
3. Composition selon la revendication 1, dans laquelle ledit polymère absorbe entre 10 et 80 % d'eau à 37 degrés Celsius.
4. Composition selon la revendication 1, dans laquelle ledit diisocyanate est sélectionné dans le groupe composé d'isophorone, d'1,6-hexaméthylène ou 4,4'-méthylène bis (isocyanatocyclohexyle).
5. Composition selon la revendication 1, dans laquelle ledit diol ou ladite diamine hydrophile est sélectionné dans un groupe composé de polyéthylène glycol, de polypropylène glycol, de polyéthylène glycol aminé, de polyéthylène glycol à terminaison d'esters d'acides aminés et de copolymères séquencés de polyéthylène glycol et de polypro-

pylène glycol.

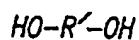
6. Composition selon la revendication 2, dans laquelle ledit diol ou ladite diamine aliphatique est sélectionné dans un groupe composé d'éthylène glycol, de propylène glycol, de 1-3 propane-diol et de 1-3 diaminopropane.
7. Composition selon la revendication 1, dans laquelle ledit silicone est sélectionné dans le groupe composé de siloxane à terminaison amino propyldiméthyl, de siloxane à terminaison carboxy propyl-dimethoxy et de siloxane à terminaison carbinol.
8. Composition selon la revendication 2, dans laquelle le polymère est obtenu à partir des produits de réaction d'environ 50 pour cent en mole de diisocyanate, 5 à 45 pour cent en mole de diol ou de diamine hydrophile, 5 à 45 pour cent en mole de diol ou diamine aliphatique et 5-40 pour cent en mole de silicone.
9. Composition selon la revendication 5, dans laquelle le polyéthylène glycol présente un poids moléculaire moyen de 600.
10. Composition selon la revendication 3, dans laquelle ledit polymère absorbe entre 20 et 70 % d'eau à 37 degrés Celsius.
11. Composition selon la revendication 1, dans laquelle la diamine hydrophile contient du silicone.
12. Bio-capteur implantable permettant de mesurer la réaction d'une substance à analyser avec l'oxygène, ledit bio-capteur ayant une membrane biocompatible permettant de contrôler la perméabilité à la substance à analyser et à l'oxygène des éléments du bio-capteur, ladite membrane comprenant une composition homogène de polymères, laquelle est perméable au glucose et à l'eau et comprenant les produits de réaction d'au moins un diisocyanate, un diol ou une diamine hydrophile et un silicone.
13. Biocapteur selon la revendication 12, dans lequel la substance à analyser contient du glucose.
14. Bio-capteur selon la revendication 13, dans lequel la composition homogène de polymères contient, par ailleurs, au moins un diol ou une diamine aliphatique ajouté(e) à la réaction.
15. Bio-capteur selon la revendication 14, dans lequel le polymère comprend 50 pour cent en mole de diisocyanate, 5 à 45 pour cent en mole de diol ou diamine hydrophile, 5 à 45 pour cent en mole de diol ou diamine aliphatique et 5-40 pour cent en mole de silicone.
16. Bio-capteur selon la revendication 12, dans lequel la composition homogène de polymères est telle que définie dans toutes les revendications 3 à 7 et 9 à 11.

## HEXAMETHYLENE DIISOCYANATE



+

DIOL



+

DIAMINO SILANE

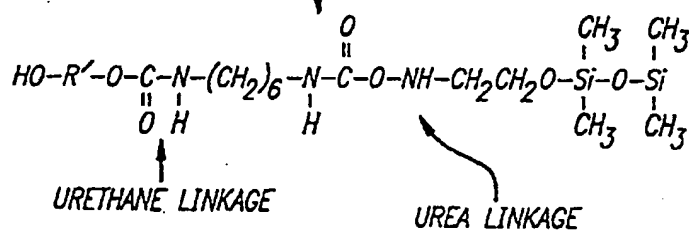
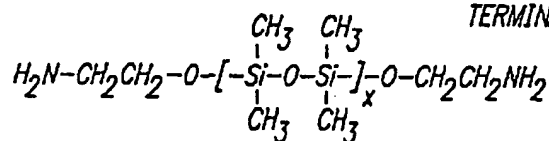
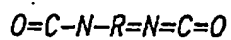
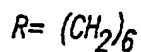
(AN AMINOPROPYLDIMETHYL  
TERMINATED SILOXANE)

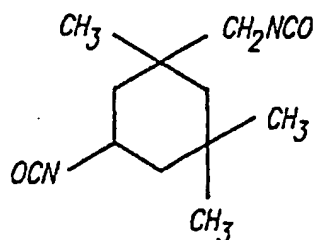
FIG. 2



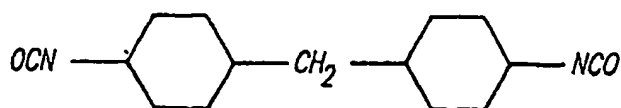
DIISOCYANATE



HEXAMETHYLENE DIISOCYANATE



ISOPHORONE DIISOCYANATE



4,4'-METHYLENEBIS(CYCLOHEXYL ISOCYANATE)

FIG. 3

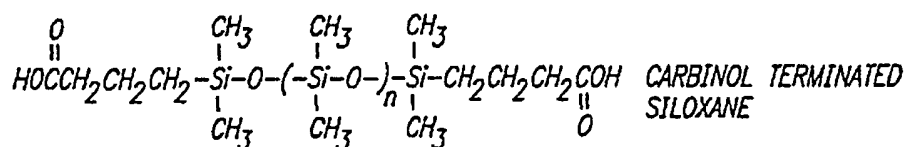
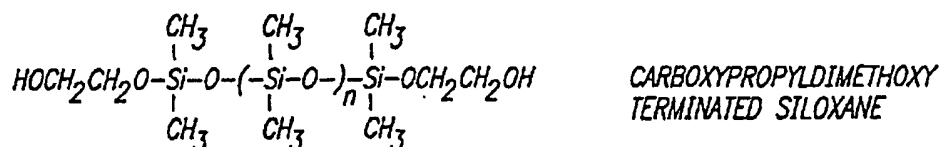
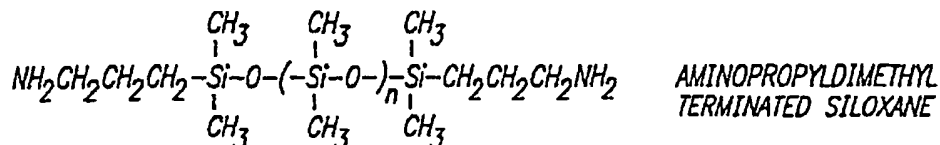


FIG. 4

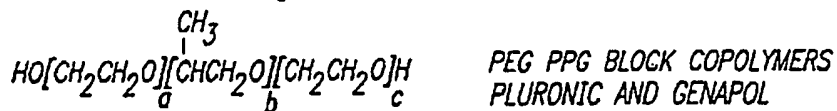
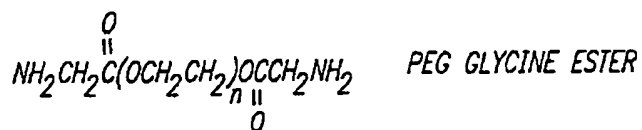
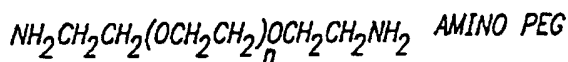


FIG. 5

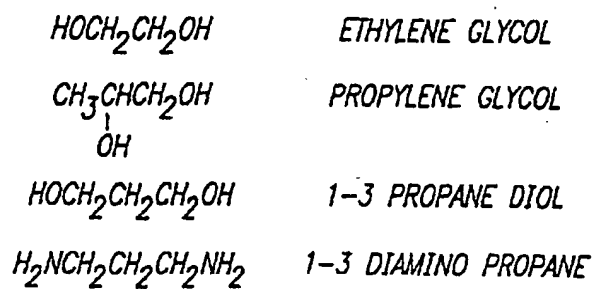
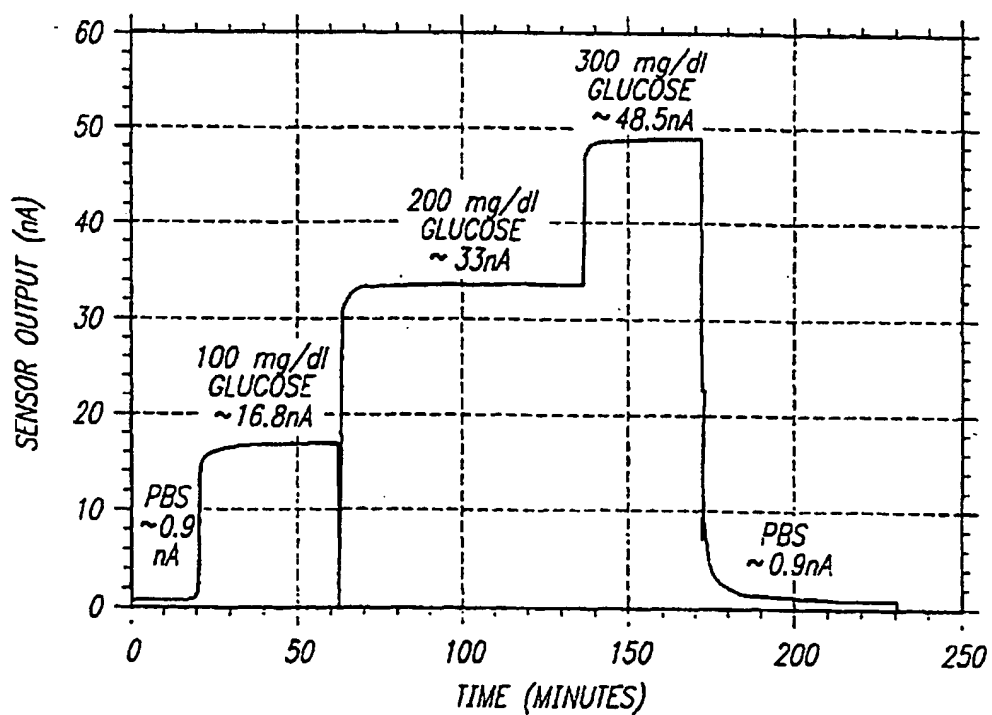


FIG. 8



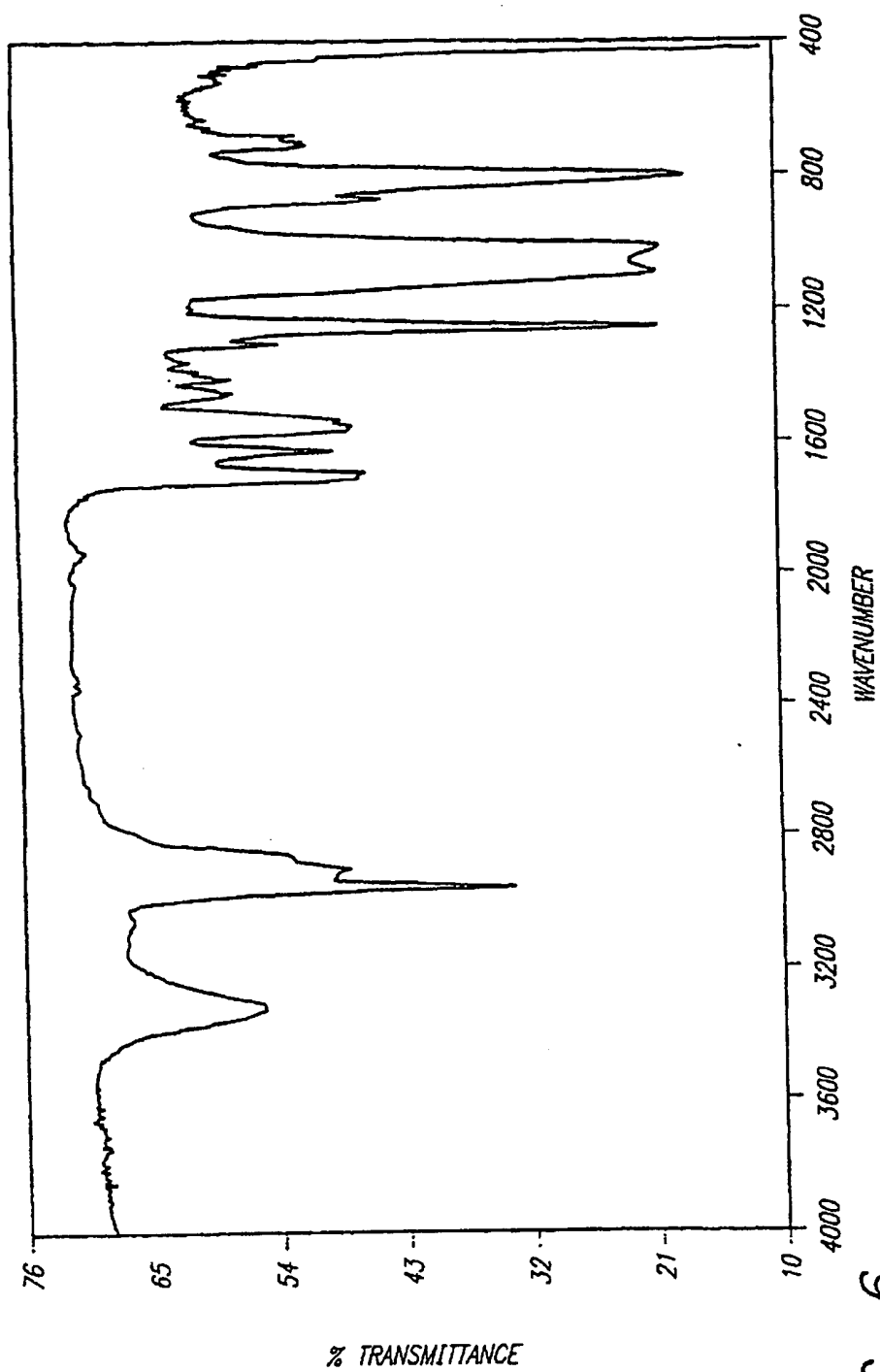


FIG. 6

FIG. 7A

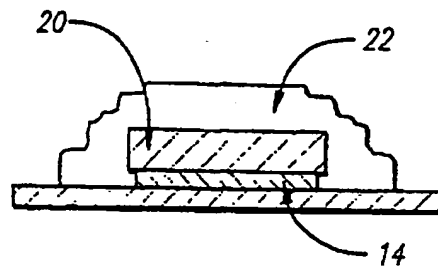
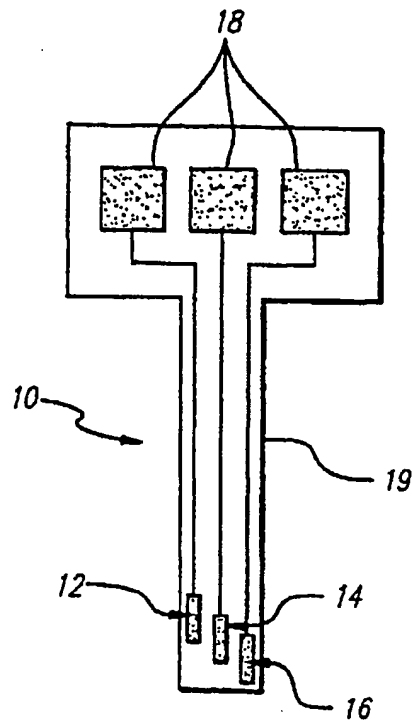


FIG. 7B

**THIS PAGE BLANK (USPTO)**



**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

**THIS PAGE BLANK (USPTO)**